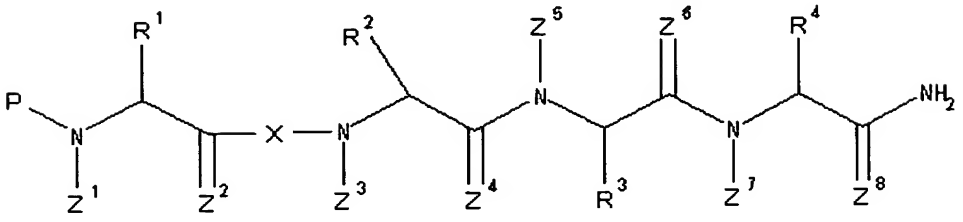
CLAIMS

1. A metastin derivative represented by formula (I):



[wherein,

each of Z^1, Z^3, Z^5 and Z^7 represents hydrogen atom or a C_{1-3} alkyl group; each of Z^2, Z^4, Z^6 and Z^8 represents hydrogen atom, O or S;

R^1 represents (1) hydrogen atom, or (2) a C_{1-8} alkyl group optionally substituted with a substituent selected from the group consisting of an optionally substituted carbamoyl group, an optionally substituted hydroxyl group and an optionally substituted aromatic cyclic group;

R^2 represents (1) hydrogen atom or (2) a cyclic or linear C_{1-10} alkyl group, or (3) a C_{1-10} alkyl group consisting of a cyclic alkyl group and a linear alkyl group;

R^3 represents:

(1) a C_{1-8} alkyl group having an optionally substituted basic group and optionally having an additional substituent,

(2) an aralkyl group having an optionally substituted basic group and optionally having an additional substituent,

(3) a C_{1-4} alkyl group having a non-aromatic cyclic hydrocarbon group of carbon atoms not greater than 7 having an optionally substituted basic group, and optionally having an additional substituent, or,

(4) a C_{1-4} alkyl group having a non-aromatic heterocyclic group of carbon atoms not greater than 7 having an optionally substituted basic group, and optionally having an additional substituent;

R^4 represents a C_{1-4} alkyl group, which may optionally be substituted with a substituent selected from the group consisting of:

(1) an optionally substituted C_{6-12} aromatic hydrocarbon group,

(2) an optionally substituted 5- to 14-membered aromatic heterocyclic

group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms,

(3) an optionally substituted C_{8-14} aromatic fused-ring group,

(4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms,

(5) an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7, and,

(6) an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7;

X represents a group shown by formula: $-NHCH(Q^1)YQ^2C(=Z^9)-$ (wherein, Q^1 represents a C_{1-4} alkyl group, which may optionally be substituted with a substituent selected from the group consisting of:

(1) an optionally substituted C_{6-12} aromatic hydrocarbon group,

(2) an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms,

(3) an optionally substituted C_{8-14} aromatic fused-ring group,

(4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms,

(5) an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7, and,

(6) an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7;

Q^2 represents (1) CH_2, which may optionally be substituted with a C_{1-4} alkyl group optionally substituted with a substituent selected from the group consisting of carbamoyl group and hydroxyl group, (2) NH, which may optionally be substituted with a C_{1-4} alkyl group optionally substituted with a substituent selected from the group consisting of carbamoyl group and hydroxyl group, or (3) O;

Y represents a group shown by formula: -CONH-, -CSNH-, $-CH_2NH-$, -NHCO-, $-CH_2O-$, $-CH_2S-$ or $-CH_2CH_2-$, which may optionally be substituted with a C_{1-6} alkyl group; and,

Z^9 represents hydrogen atom, O or S); and,

P represents:

(1) hydrogen atom;

(2) an optional amino acid residue continuously or discontinuously bound from the C-terminal end of the 1-48 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 1;

(3) a group represented by formula:

J^1-J^2-$C(J^3)(Q^3)Y^1C(J^4)(Q^4)Y^2C(J^5)(Q^5)Y^3C(J^6)(Q^6)C(=Z^{10})$-

(wherein,

J^1 represents (a) hydrogen atom or (b) (i) a C_{1-15} acyl group, (ii) a C_{1-15} alkyl group, (iii) a C_{6-14} aryl group, (iv) a carbamoyl group, (v) a carboxyl group, (vi) a sulfino group, (vii) an amidino group or (viii) a glyoxyloyl group, which group may optionally be substituted with (a) hydrogen atom, or (b) a substituent containing an optionally substituted cyclic group;

J^2 represents (1) NH optionally substituted with a C_{1-6} alkyl group, (2) CH_2 optionally substituted with a C_{1-6} alkyl group, (3) O or (4) S;

each of J^3 through J^6 represents hydrogen atom or a C_{1-3} alkyl group;

each of Q^3 through Q^6 represents a C_{1-4} alkyl group, which may optionally be substituted with a substituent selected from the group consisting of:

(1) an optionally substituted C_{6-12} aromatic hydrocarbon group,

(2) an optionally substituted 5- to 14-membered aromatic heterocyclic group consisting of 1 to 7 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms,

(3) an optionally substituted C_{8-14} aromatic fused-ring group,

(4) an optionally substituted 5- to 14-membered aromatic fused heterocyclic group consisting of 3 to 11 carbon atoms and hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms,

(5) an optionally substituted non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7,

(6) an optionally substituted non-aromatic heterocyclic group having carbon atoms not greater than 7,

(7) an optionally substituted amino group,

(8) an optionally substituted guanidino group,

(9) an optionally substituted hydroxyl group,

(10) an optionally substituted carboxyl group,

(11) an optionally substituted carbamoyl group, and

(12) an optionally substituted sulfhydryl group,

or hydrogen atom;

J^3 and Q^3, J^4 and Q^4, J^5 and Q^5 or J^6 and Q^6 may be combined together, or, J^2 and Q^3, Y^1 and Q^4, Y^2 and Q^5, or Y^3 and Q^6 may be combined together, to form a ring;

each of Y^1 through Y^3 represents a group represented by formula: $-CON(J^{13})-$, $-CSN(J^{13})-$, $-C(J^{14})N(J^{13})-$ or $-N(J^{13})CO-$ (wherein each of J^{13} and J^{14} represents hydrogen atom or a C_{1-3} alkyl group); and,

Z^{10} represents hydrogen atom, O or S);

(4) a group represented by formula:

J^1-J^2-$C(J^7)(Q^7)Y^2C(J^8)(Q^8)Y^3C(J^9)(Q^9)C(=Z^{10})$-

(wherein,

J^1 and J^2 have the same significance as described above;

J^7 through J^9 have the same significance as J^3;

Q^7 through Q^9 have the same significance as Q^3;

Y^2 and Y^3 have the same significance as described above;

Z^{10} has the same significance as described above;

J^7 and Q^7, J^8 and Q^8 or J^9 and Q^9 may be combined together, or, J^2 and Q^7, Y^2 and Q^8 or Y^3 and Q^9 may be combined together, to form a ring);

(5) a group represented by formula:

J^1-J^2-$C(J^{10})(Q^{10})Y^3C(J^{11})(Q^{11})C(=Z^{10})$-

(wherein,

J^1 and J^2 have the same significance as described above represents;

J^{10} and J^{11} have the same significance as J^3;

Q^{10} and Q^{11} have the same significance as Q^3;

Y^3 has the same significance as described above;

Z^{10} has the same significance as described above; and,

J^{10} and Q^{10} or J^{11} and Q^{11} may be combined together, or J^2 and Q^{10} or Y^3 and Q^{11} may be combined together, to form a ring);

(6) a group represented by formula: J^1-J^2-C(J^{12})(Q^{12})C(=Z^{10})-

(wherein,

J^1 and J^2 have the same significance as described above;

J^{12} has the same significance as J^3;

Q^{12} has the same significance as Q^3;

Z^{10} has the same significance as described above; and,

J^{12} and Q^{12} may be combined together, or J^2 and Q^{12} may be combined together, to form a ring); or,

(7) a group represented by formula: J^1- (wherein, J^1 has the same significance as described above)] (provided that a peptide consisting of the amino acid sequence of 1-54, 2-54, 3-54, 4-54, 5-54, 6-54, 7-54, 8-54, 9-54, 10-54, 11-54, 12-54, 13-54, 14-54, 15-54, 16-54, 17-54, 18-54, 19-54, 20-54, 21-54, 22-54, 23-54, 24-54, 25-54, 26-54, 27-54, 28-54, 29-54, 30-54, 31-54, 32-54, 33-54, 34-54, 35-54, 36-54, 37-54, 38-54, 39-54, 40-54, 41-54, 42-54, 43-54, 44-54, 45-54, 46-54, 47-54, 48-54 or 49-54 in the amino acid sequence represented by SEQ ID NO: 1 is excluded), or a salt thereof.

2. The metastin derivative (I) according to claim 1 or a salt thereof, which is:

(i) D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 141),

(ii) D-Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 174),

(iii) 3-(3-Indolyl)propionyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 260),

(iv) 3-Phenylpropionyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 269),

(v) 2-(indol-3-yl)ethylcarbamoyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 279),

(vi) D-Tyr-Asn-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 286),

(vii) D-Tyr-Asn-Trp-Asn-Ser-PheΨ(CSNH)Gly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 296),

(viii) TyrΨ(CH_2NH)Asn-D-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 300),

(ix) D-Tyr-D-Asn-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 303),

(x) D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 305),

(xi) D-Tyr-Asn-Trp-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe(4F)-NH_2 (Compound No. 318),

(xii) D-Tyr-Asn-Trp-Asn-Ser-PheΨ(NHCO)Gly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 319),

(xiii) 3-Pyridylpropionyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 322),

(xiv)4-Imidazoleacetyl-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Phe-NH_2 (Compound No. 323),

(xv) D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 385), or

(xvi) D-Tyr-D-Pya(4)-Asn-Ser-Phe-AzaGly-Leu-Arg(Me)-Trp-NH_2 (Compound No. 386).

3. A prodrug of the metastin derivative (I) according to claim 1 or a salt thereof.

4. A pharmaceutical comprising the metastin derivative (I) according to claim 1 or a salt thereof, or a prodrug thereof.

5. The pharmaceutical according to claim 4, which is an agent for suppressing cancer metastasis or an agent for suppressing cancer proliferation.

6. The pharmaceutical according to claim 4, which is an agent for preventing/treating cancer.

7. The pharmaceutical according to claim 4, which is an agent for regulating a function of the pancreas.

8. The pharmaceutical according to claim 4, which is an agent for preventing/treating acute or chronic pancreatitis or pancreatic cancer.

9. The pharmaceutical according to claim 4, which is an agent for regulating a function of the placenta.

10. The pharmaceutical according to claim 4, which is an agent for preventing/treating choriocarcinoma, hydatid mole, invasive mole, miscarriage, fetal hypoplasia, abnormal glucose metabolism, abnormal lipid metabolism or labor induction.

11. The pharmaceutical according to claim 4, which is an agent for improving gonadal function.

12. The pharmaceutical according to claim 4, which is an agent for preventing/treating hormone-dependent cancer, infertility, endometriosis or myoma of the uterus.

13. The pharmaceutical according to claim 4, which is an agent for inducing or stimulating ovulation.

14. The pharmaceutical according to claim 4, which is a gonadotropic hormone secretagogue agent or a sex hormone secretagogue agent.

15. The pharmaceutical according to claim 4, which is an agent for preventing/treating Alzheimer's disease or moderate cognitive impairment.

16. A method for suppressing cancer metastasis or cancer proliferation, which comprises administering to a mammal an effective dose of the metastin derivative (I) according to claim 1 or a salt thereof, or a prodrug thereof.

17. A method for preventing/treating cancer, which comprises administering to a mammal an effective dose of the metastin derivative (I) according to claim 1 or a salt thereof, or a prodrug thereof.

18. A method for regulating a function of the pancreas, which comprises administering to a mammal an effective dose of the metastin derivative (I) according to claim 1 or a salt thereof, or a prodrug thereof.

19. A method for preventing/treating acute or chronic pancreatitis or pancreatic cancer, which comprises administering to a mammal an effective dose of the metastin derivative (I) according to claim 1 or a salt thereof, or a prodrug thereof.

20. A method for regulating a function of the placenta, which comprises administering to a mammal an effective dose of the metastin derivative (I) according to claim 1 or a salt thereof, or a prodrug thereof.

21. A method for preventing/treating choriocarcinoma, hydatid mole, invasive mole, miscarriage, fetal hypoplasia, abnormal glucose metabolism, abnormal lipid metabolism or labor induction, which comprises administering to a mammal an effective dose of the metastin derivative (I) according to claim 1 or a salt thereof, or a prodrug thereof.

22. A method for improving gonadal function, which comprises administering to a mammal an effective dose of the metastin derivative (I) according to claim 1 or a salt thereof, or a prodrug thereof.

23. A method for preventing/treating hormone-dependent cancer, infertility, endometriosis or myoma of the uterus, which comprises administering to a mammal

an effective dose of the metastin derivative (I) according to claim 1 or a salt thereof, or a prodrug thereof.

24. A method for inducing or stimulating ovulation, which comprises administering to a mammal an effective dose of the metastin derivative (I) according to claim 1 or a salt thereof, or a prodrug thereof.

25. A method for promoting gonadotropic hormone secretion or promoting sex hormone secretion, which comprises administering to a mammal an effective dose of the metastin derivative (I) according to claim 1 or a salt thereof, or a prodrug thereof.

26. A method for preventing/treating Alzheimer's disease or moderate cognitive impairment, which comprises administering to a mammal an effective dose of the metastin derivative (I) according to claim 1 or a salt thereof, or a prodrug thereof.

27. Use of the metastin derivative (I) according to claim 1 or a salt thereof, or a prodrug thereof to manufacture an agent for suppressing cancer metastasis or an agent for suppressing cancer proliferation.

28. Use of the metastin derivative (I) according to claim 1 or a salt thereof, or a prodrug thereof to manufacture an agent for preventing/treating cancer.

29. Use of the metastin derivative (I) according to claim 1 or a salt thereof, or a prodrug thereof to manufacture an agent for regulating a function of the pancreas.

30. Use of the metastin derivative (I) according to claim 1 or a salt thereof, or a prodrug thereof to manufacture an agent for preventing/treating acute or chronic pancreatitis or pancreatic cancer.

31. Use of the metastin derivative (I) according to claim 1 or a salt thereof, or a prodrug thereof to manufacture an agent for regulating a function of the placenta.

32. Use of the metastin derivative (I) according to claim 1 or a salt thereof, or a prodrug thereof to manufacture an agent for preventing/treating choriocarcinoma, hydatid mole, invasive mole, miscarriage, fetal hypoplasia, abnormal glucose metabolism, abnormal lipid metabolism or labor induction.

33. Use of the metastin derivative (I) according to claim 1 or a salt thereof, or a prodrug thereof to manufacture an agent for improving gonadal function.

34. Use of the metastin derivative (I) according to claim 1 or a salt thereof, or a prodrug thereof to manufacture an agent for preventing/treating

hormone-dependent cancer, infertility, endometriosis or myoma of the uterus.

35. Use of the metastin derivative (I) according to claim 1 or a salt thereof, or a prodrug thereof to manufacture an agent for inducing or stimulating ovulation.

36. Use of the metastin derivative (I) according to claim 1 or a salt thereof, or a prodrug thereof to manufacture a gonadotropic hormone secretagogue agent or a sex hormone secretagogue agent.

37. Use of the metastin derivative (I) according to claim 1 or a salt thereof, or a prodrug thereof to manufacture an agent for preventing/treating Alzheimer's disease or moderate cognitive impairment.

38. A pancreatic glucagon secretagogue agent, comprising an agonist for a metastin receptor.

39. An agent for promoting urine formation, comprising an agonist for a metastin receptor.

40. An agent for preventing/treating obesity, hyperlipemia, type II diabetes mellitus, hypoglycemia, hypertension, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, edema, urinary disturbances, insulin resistance, unstable diabetes, fatty atrophy, insulin allergy, insulinoma, arteriosclerosis, thrombotic disorders or lipotoxicity, comprising an agonist for a metastin receptor.

41. The agent according to claim 38 through 40, wherein the agonist for a metastin receptor is the metastin derivative (I) according to claim 1 or a salt thereof, or a prodrug thereof.

42. A method for promoting pancreatic glucagon secretion, which comprises administering to a mammal an effective dose of the agonist for a metastin receptor.

43. A method for promoting urine formation, which comprises administering to a mammal an effective dose of the agonist for a metastin receptor.

44. A method for preventing/treating obesity, hyperlipemia, type II diabetes mellitus, hypoglycemia, hypertension, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, edema, urinary disturbances, insulin resistance, unstable diabetes, fatty atrophy, insulin allergy, insulinoma, arteriosclerosis, thrombotic disorders or lipotoxicity, which comprises administering to a mammal an effective dose of the agonist for a metastin receptor.

45. Use of the agonist for a metastin receptor to manufacture a pancreatic glucagon secretagogue agent.

46. Use of the agonist for a metastin receptor to manufacture an agent for

promoting urine formation.

47. Use of the agonist for a metastin receptor to manufacture an agent for preventing/treating obesity, hyperlipemia, type II diabetes mellitus, hypoglycemia, hypertension, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, edema, urinary disturbances, insulin resistance, unstable diabetes, fatty atrophy, insulin allergy, insulinoma, arteriosclerosis, thrombotic disorders or lipotoxicity.